SYNTHESIS OF *B*-ALKYLATED OXAZABOROLIDINES DERIVED FROM EPHEDRINE AND NOREPHEDRINE

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Claim of Priority:

This application claims the benefit of U.S. Provisional Application No. 60/445,743, filed February 7, 2003, which is incorporated herein by reference in its entirety.

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Background of the Invention:

Chiral 1,3,2-oxazaborolidines have been well studied and regarded as important catalysts or reagents for the enantioselective reduction of prochiral ketones, imines and oximes, and in other stereoselective transformations. The development of oxazaborolidines has been driven mainly by the

availability of suitable chiral aminoalcohols. Norephedrine and ephedrine are commercially available and relatively inexpensive in the two enantiomeric forms, and their derived oxazaborolidines have been reported as efficient chiral templates for the borane reduction of prochiral ketones and C=N double bonds, in catalytic hydroborations, as well as in additions of diethylzinc to aldehydes.

B-H oxazaborolidines are usually prepared by the reaction of norephedrine or ephedrine with borane-THF or borane dimethylsulfide complex. Their extreme sensitivity to air and moisture make these reagents difficult to purify by distillation or recrystallization and, consequently, they are commonly prepared *in situ* for subsequent reactions. However, side products present with the unpurified *B*-H heterocyclic catalysts or reagents cause a detrimental effect on the enantiomeric purity of desired chiral products. Furthermore, *B*-H oxazaborolidines can form dimers that alter the nature of the chiral catalyst. On the contrary, *B*-alkylated compounds are more stable, easier to purify and handle than the nonsubstituted counterparts, and produce similar enantioselectivities. *B*-substituted 1,3,2-oxazaborolidines are typically prepared by condensation of the aminoalcohols with boronic acids, boroxines, or their boronate esters, by removing water and boronic acid, or boronic ester residues, by azeotropic distillation in toluene. The treatment of chiral aminoalcohols with organo-bis(diisopropylamino)borane for the synthesis of *B*-alkyl and phenyl oxazaborolidines has also been reported. However, these methods require expensive and elaborated reagents, and moreover, the complete removal of water and boronic acid, or it derivatives, is extremely difficult.

Such methods are disclosed by and through the following references, each of which are incorporated herein by reference in their entirety:

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Summary of the Invention:

Pure *B*-alkyl-1,3,2-oxazaborolidines are derived from ephedrine and norephedrine via alkylation of the parent boraheterocyclic compound. According to one aspect of the invention, the reaction is performed by means of a one-pot synthesis. A preferred method is shown in Fig. 1, where R = H or Me and R^1 = Me or n-Bu.

Brief Description of the Drawings:

Fig. 1 is a schematic diagram showing one preferred synthesis of pure *B*-alkyl-1,3,2-oxazaborolidines.

Fig. 2 is a schematic diagram showing one preferred synthesis of 4b. (4S,5R)-*B*-4-methyl-5-phenyl-[1,3,2]-oxazaborolidine

Fig. 3a is a schematic diagram of intermediate, Methyl boronic mono ester of (1R,2S)-2-

amino-1-phenyl-propan-1-ol or, of norephedrine, prepared in accordance with synthesis shown in Fig. 2.

Fig. 3b is a schematic diagram of intermediate, Butyl boronic mono ester of (1R,2S)-2-amino-1-phenyl-propan-1ol or, of norephedrine, prepared in accordance with synthesis shown in Fig. 2.

Fig. 3c is a schematic diagram of intermediate, Methyl boronic mono ester of (1R,2S)-2-methylamino-1-phenyl-propan-1-ol or, of ephedrine, prepared in accordance with synthesis shown in Fig. 2.

Fig. 3d is a schematic diagram of the intermediate, Butyl boronic mono ester of (1R,2S)-2-methylamino-1-phenyl-propan-1-ol or, of ephedrine, prepared in accordance with synthesis shown in Fig. 2.

Fig. 4a is a schematic diagram of the product, (4S,5R)-2,4-Dimethyl-5-phenyl-[1,3,2]oxazaborolidine, prepared in accordance with synthesis shown in Fig. 1 and Fig. 2.

Fig. 4b is a schematic diagram of the product, (4S,5R)-2-Butyl-4-methyl-5-phenyl-[1,3,2]oxazaborolidine, prepared in accordance with synthesis shown in Fig. 1 and Fig.2.

Fig. 4c is a schematic diagram of the product, (4S,5R)-2,3,4-Trimethyl-5-phenyl-[1,3,2]oxazaborolidine, prepared in accordance with synthesis shown in Fig. 1 and Fig. 2.

Fig. 4d is a schematic diagram of the product, (4S,5R)-2-Butyl-3,4-dimethyl-5-phenyl-[1,3,2]oxazaborolidine, prepared in accordance with synthesis shown in Fig. 1 and Fig. 2.

Fig. 5 is a schematic diagram of the products: (a): (4S,5R)-2-sec-Butyl-3-methyl-5-phenyl-[1,3,2]oxazaborolidine, where R= sec-butyl and R^1 = H; and (b): (4S,5R)-2-sec-Butyl-3,4-dimethyl-5-phenyl-[1,3,2]oxazaborolidine, where R= sec-butyl; R^1 = Me, prepared in accordance with synthesis shown in Fig. 1.

Fig. 6a is a schematic diagram of the product, having a family name of: B-methyl or B-butyl-1-[1,3,2]-oxazaborolidine derived from (1S,2R)-1,2-diphenylethanol, prepared in accordance with synthesis shown in Fig. 1. For R= Me, the specific name is (4S,5R)-2-Methyl-3,5-diphenyl-[1,3,2]oxazaborolidine; For R= Butyl, the specific name is (4S,5R)-2- Butyl-3,5-diphenyl-[1,3,2]oxazaborolidine.

Fig. 6b is a schematic diagram of the product, having a family name of: Lithium borohydrides of B-methyl or B-butyl- of [1,3,2]-oxazaborolidine derived from (1S,2R)-1,2-diphenylethanol, prepared in accordance with synthesis shown in Fig. 1. For R= Me, the specific name is (4S,5R)-2-Methyl-3,5-diphenyl-[1,3,2]oxazaborolidine lithium hydride; For R= Butyl, the specific name is (4S,5R)-2- Butyl-3,5-diphenyl-[1,3,2]oxazaborolidine lithium hydride.

Fig. 7a is a schematic diagram of the product, having a family name of ***B***-methyl or ***B***-butyl- 1-[1,3,2]-oxazaborolidine derived from (1R,2RS)-*cis*-1,2-amino indanol, prepared in accordance with synthesis shown in Fig. 1. For R = Me, the specific name is 2-Methyl-3,3a,8,8a-tetrahydro-2H-1-oxa-3-aza-2-bora-cyclopenta[a]indene. For R= Bu, the specific name is 2-Butyl-3,3a,8,8a-tetrahydro-2H-1-oxa-3-aza-2-bora-cyclopenta[a]indene.

Fig. 7b is a schematic diagram of the product, having a family name of Lithium borohydrides of ***B***-methyl or ***B***-butyl- 1-[1,3,2]-oxazaborolidine derived from (1R,2S)-*cis*-1,2-amino indanol, prepared in accordance with synthesis shown in Fig. 1. For R = Me, the specific name is 2-Methyl-3,3a,8,8a-tetrahydro-2H-1-oxa-3-aza-2-bora-cyclopenta[a]indene lithium borohydride; For R= Bu, the specific name is 2-Butyl-3,3a,8,8a-tetrahydro-2H-1-oxa-3-aza-2-bora-cyclopenta[a]indene lithium borohydride.

Fig. 8a is a schematic diagram of the product, having a family name of ***B***-butyl of [1,3,2]-

oxazaborolidine, derived from (S)-α,α-diphenyl prolinol, prepared in accordance with synthesis shown in Fig. 1. The specific name is (S)-1-Butyl-3,3-diphenyl-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole.

Fig. 8b is a schematic diagram of the product, having a family name of Lithium borohydrides of *B*-butyl of [1,3,2]-oxazaborolidine derived from (S)-α,α-diphenyl prolinol, prepared in accordance with synthesis shown in Fig. 1. The specific name is (S)-1-Butyl-3,3-diphenyl-tetrahydropyrrolo[1,2-*c*][1,3,2]oxazaborole lithium hydride.

Detailed Description of the Invention:

With reference to Fig. 2, one preferred method of *B*-alkylation of an oxazaborolidine is described. The oxazaborolidine 1 is derived from (1R, 2S)(-)-norephedrine by the n-butyllithium addition, forming the corresponding borohydride 2b. After an aqueous work-up, the borate acid 3b was isolated as a clear oil. This intermediate 3b was observed to be remarkably stable to acid and base hydrolysis; it can act as a source for the heterocyclic catalyst. The formation of product 4b was successfully completed by heating neat intermediate 3b, obtaining a 75% yield of the distilled product with more than 95% purity.

A preferred synthesis procedure according to Fig. 1, follows. To a solution of Borane-THF (43 mmol, 43 mL, 1.0 M) at room temperature was added drop-wise a solution of (1R,2S)(-) norephedrine (2.5 g, 15.5 mmol) in THF (25 mL). After the clear reaction mixture was stirred for 12 hours at room temperature, the solvents were removed under vacuum (20 mmHg) and the white foamy residue was gradually heated in an oil bath to 130°C and maintained at this temperature for 30 min. A clear crystalline solid compound was obtained, with properties similar to the B-H-1,3,2-

oxazaborolidine reported by Quallich in U.S. Patent No. 6,037,505, May 14, 2000. A solution of n-BuLi (18.6 mmol, 8.0 mL, 2.32 M in hexanes) was added in 15 minutes to the previously obtained solid dissolved in anhydrous ether (30 mL) and cooled at -78°C. The mixture was stirred overnight at 25°C. The pale rose mixture with a fine suspension was cooled at 0°C and then allowed to react with solid ammonium chloride (4.4g, 82.5 mmol) for 4 hours at room temperature. The solid was removed by filtration using a Schlenk filter under nitrogen flow and vacuum (15 mmHg). The filtrated was concentrated using a vacuum pump and heated at 40°C obtaining the crude product (3.9g, 99% yield). A short path distillation at reduced pressure furnished the pure *B*-butyl-1,3,2-oxazaborolidine 4b as a clear oil. Its properties were measured as follows: 2.0 g, 56%, 98% purity by GC/MS; Bp 82 °C/0.1 mmHg; IR(ν cm^{-1}) 3219(NH); B NMR (500 MHz), δ ($CDCl_3$, ppm) 35; H δ 7.3 (m, 5H), 7.50 (d, J = 6 Hz, 1H), 3.9 (m, 1H), 3.48 (br s, 1H, NH), 1.5 (m, 4H), 0.9 (m, 5H), 0.6 (d, J = 6 Hz, 3H); C δ 139.6, 127.7, 127.2, 126.7, 126.1, 82.1, 53.8, 27.3, 25.4, 20.4, 13.8, 11.3 (br); MS(m/z): 216.9 ($M^{+\cdot}$), 202 (100%).

With reference to Figs. 3a-3d and 4a-4d, the synthesis of four *B*-alkyl-1,3,2-oxazaborolidines is further described. With reference to these figures, the compounds shown in Figs. 3a-3d illustrate the intermediate product of the synthesis and the compounds shown in Figs. 4a-4d illustrate the resulting product of the respective intermediate (*e.g.* the product shown in Fig. 4a is derived from the intermediate shown in Fig. 3a).

The same approach (as described above with reference to Fig. 2) for these synthesis were applied for the preparation of the other *B*-alkyl 1,3,2-oxazaborolidines derived from (1R, 2S)(-)-norephedrine and (1R, 2S)-(-)-ephedrine, which are shown in Figs. 4a-4d. In general, the *B*-H oxazaborolidines were synthesized following the established condensation reaction of the

corresponding chiral 1,2-amino alcohol with borane-THF. The boron alkylation with *n*-butyl-, or methyllithium, of the *in situ* prepared *B*-H oxazaborolidine took place readily at -78°C, forming the corresponding lithium borohydride salt 2 (as shown in Fig. 1). Upon treatment with an aqueous ammonium chloride solution, extraction with ether or dichloromethane, and drying the organic phase with sodium sulfate, produced the crude borate acid-amine complexes 3 (also shown in Fig. 1) with high purity and excellent yield. The *B*-butyl oxazaborolidine derived from norephedrine was obtained in good yield when the borate acid shown in Fig. 3b was heated under reduced pressure during distillation. In the case of analogues shown in Figs. 3a, 3c and 3d, the yields of the pure *B*-alkyloxazaborolidines obtained by the same dehydration method were modest, since a significant amount of the intermediate also codistilled with the oxazaborolidine and afterwards the pure intermediates shown in Figs. 3a, 3c and 3d were obtained. The yields of the desired heterocyclic products were improved by azeotropic distillation using toluene or xylene and 4 Δ molecular sieves to remove water. Accordingly, this process is preferred for these compounds.

A nonaqueous direct alternative to prepare the *B* alkylated oxazaborolidine from the borohydride intermediate 2 (shown in Fig. 1) by treatment with MeI or TMSCl did not yield optimal results. However, the use of anhydrous ammonium chloride provided the expected oxazaborolidines in good yield and with excellent purity as indicated by GC/MS, B, H and C NMR. The B NMR signals and boiling points of intermediates and *B*-methyl and n-butyl substituted oxazaborolidines, and the isolated yields of the analytical pure compounds prepared by the aqueous and dry methods, are identified in table 1 for the intermediates shown in Figs. 3a, 3b, 3c and 3d and the resulting products shown in Figs. 4a, 4b, 4c and 4d.

Table 1

Int. (Fig. #)	^{11}B-NMR (ppm)[a]	Bp. (°C/mmHg)	Yield (%)[b]	Product (Fig. #)	^{11}B-NMR (ppm)[a]	Bp. (°C/mmHg)	Yield (%)[c]	Yield (%)[c]
3a	7.1	95/0.7	80	4a	32	42/0.12	48[d]	65[f]
3b	8.0		91	4b	35	82/0.1	75[d]	56[f]
3c	8.1	120/0.5	75	4c	34	80/2.0	45[d]	58[f]
3d	8.5	110/0.1	97	4d	34	84/0.55	50[d]	70[f]

With respect to Table 1, the first column identifies the intermediate by reference to the figure in which it is shown. The second column identifies chemical displacements of the respective intermediate using BF_3-OEt_2 as an internal standard. The third column identifies the boiling point of the intermediate measured in °C per millimetre of mercury. The fourth column identifies the crude yield of the intermediate. The fifth column identifies the final product by reference to the figure in which it is shown. The sixth column identifies chemical displacements of the respective product using BF_3-OEt_2 as an internal standard. The seventh and eight columns identify the yields of isolated products purified by distillation and characterized by their spectral data. The seventh column, in particular, identifies the yield by treatment with aqueous ammonium chloride and calculated by crude product. The eighth column, in particular, identifies the yield by treatment with anhydrous ammonium chloride.

According to a further aspect of the invention, the above methods extend to other *B*-substituents such as *sec*-butyl derived from ephedrine and norephedrine. The corresponding

oxazaborolidines have been obtained in good yield and with high purity (98%) as clear oils after vacuum distillation. In addition, the methods extend to the alkylation of the B-H oxazaborolidine of norephedrine using organomagnesium (BuMgBr) reagents instead of lithium reagent. This method permits the synthesis of a wide variety of B-alkyl substituents.

In addition, other oxazaborolidines derived from chiral amino alcohols such as, (1*S*,2*R*)-1,2-diphenyl-2-aminoethanol(1*R*,2*S*)-1,2-amino indanol and (*S*)∀,∀-diphenyl prolinol have been prepared, in somewhat lower yields, according to the above methods. Finally, in addition to the *B*-butyl oxazaborolidine derived from (*S*)-∀,∀-diphenyl prolinol, a dimeric borane complex was isolated.

In summary, the invention achieves the first efficient and general approach to *B*-alkylated oxazaborolidines derived from ephedrine and norephedrine, by means of a general synthesis mechanism generally applicable to *B*-substituted oxazaborolidines.

Specifically, the above method applies to the synthesis of sec-butyl derivatives from ephedrine or norephedrine, as shown in Fig. 5. It also applies to the synthesis of B-methyl or butyl derivatives from (1S,2R)-1,2-diphenyl ethanol, as shown in Figs. 6a and 6b. It also applies to the synthesis of B-methyl or butyl derivatives from (1R,2S)-1,2-amino indanol, as shown in Figs. 7a and 7b. Finally it applies to the synthesis of B-butyl derivatives from (S)-alpha, alpha-diphenylprolinol, as shown in Figs. 8a and 8b.

As shown and described above, the subject invention teaches improved methods for the synthesis of *B*-alkyloxazaborolidines. These are prepared by *B* alkylation of the parent heterocyclic compound in accordance with the reaction shown in Fig. 1. Although this synthesis has been described with reference to specific compounds and by use of specific methods, those skilled in the art will appreciate that many variations and modifications are possible without departing from the scope

and spirit of the invention. In addition, for purposes of interpreting the following claims, specific reference to a compound or method should be read to encompass not only that specific compound or method but also all equivalent compounds or methods disclosed in the specification or known or which become knowable to those skilled in the art. Accordingly, the following claims should be read to include and to encompass all variations, modifications and equivalents to that which is expressly claimed.